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ATROPINE SULFATE IMPAIRS PERFORMANCE ON AN OVERTRAINED SPATIAL TASK IN A DOSE-DEPENDENT FASHION

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ABSTRACT

Twelve rats were trained to learn the location of a spatially fixed platform hidden in a Morris water maze. Accurate navigation was rewarded by escape from the water on to the platform. Asymptotic performance was achieved over six training days (10 trials/day). Then retention of the spatial task was assessed 30 minutes after treatment with 5, 25, 50, 75 or 100 mg/kg, ip, atropine sulfate or the equivalent volume of saline. There was a significant, dose-dependent, drug effect on escape latency, swim distance, swim speed and swim path measures of spatial performance. There was no significant drug effect on heading error; atropinized animals swam directly toward the escape platform over the first 12 cm of their swim path. However, treatment with atropine sulfate significantly disrupted the usual, direct swim path used to reach the hidden escape platform. Atropinized animals frequently swam within a 30 cm wide alley directly toward the platform but used one or more 360° loops to locate the platform. We suggest that cholinergic blockade may significantly disrupt the processing of distal visual cues which rats use in place navigation tasks.

Key Words: Atropine Sulfate - Spatial Retention - Morris water maze - Rat

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In conducting the research described in this report, the investigators adhered to the 'Guide for the Care and Use of Laboratory Animals,' as prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.

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Central blockade of cholinergic synapses produces an inability to use spatial mapping strategies during the acquisition of spatial tasks (Sutherland et al. 1982; Hagan et al. 1986; Stevens, 1981; Whishaw 1985; Ellen et al. 1986). However, studies of central cholinergic blockade on the retention of overtrained spatial tasks produce conflicting results (Buresova et al. 1986; Costall et al. 1988; Harley 1979; Whishaw 1985; Levy et al. 1983; Buresova and Bures 1982; Eckerman et al. 1980; Hagan et al. 1986; Rauch et al in press-a; Rauch et al. in press-b). There may, therefore, be differential cholinergic involvement in task retention as opposed to acquisition. For example, Buresova et al. (1986) reported that acquisition of a spatial task in an eight-arm radial maze was impaired by pretrial intraperitoneal (ip) injection of only 0.1 and 0.2 mg/kg, scopolamine, but a much higher dose (1.0 mg/kg, ip) was required to impair overtrained performance (i.e., escape latency). Similarly, Costall et al. (1988) reported that scopolamine (0.25 mg/kg, ip) impaired the acquisition of a spatial task in the Morris water maze but did not disrupt the retention of that task in pretrained rats. In another study, scopolamine (1 mg/kg, ip) failed to disrupt the retention of a previously acquired spatial task in a sunburst maze (Harley 1979). Whishaw (1985), using a Morris water maze, found that atropine sulfate (50 mg/kg, ip) treated rats were impaired on the acquisition of a spatial task as measured by escape latency and heading error. However, in the same study, pretrained rats were relatively unimpaired by atropine sulfate (50 mg/kg, ip) when tested on the retention of a previously acquired spatial task. Levy et al. (1983) reported that acute administration of atropine sulfate (1-6 mg/kg, sc) to mice trained on a radial arm maze task produced dose-related impairments in working memory errors, however, there was no impairment in reference memory errors at any

dose. In fact, Levy et al. (1983) showed that under some doses reference memory performance was significantly better than the saline control.

On the other hand, central cholinergic blockade with scopolamine (0.1 mg/kg) increased the number of errors on a highly overtrained working memory task using the radial arm maze (Buresova and Bures 1982; Eckerman et al. 1980). Recently, several studies (Hagan et al. 1986; Rauch et al. in press-a; Rauch et al. in press-b) have shown atropine sulfate impairs the retention of a previously acquired spatial task. Atropine sulfate (30 mg/kg) administered intravenously (iv) significantly impaired escape latency and choice accuracy measures of spatial retention in a modified multiple cross maze (Rauch et al. in press-b). In addition, when ip, subcutaneous (sc) or iv injections of equal doses of atropine sulfate (30 mg/kg) were compared on a spatial retention task in a multiple cross maze, iv and ip atropine sulfate produced significant impairments in choice accuracy (Rauch et al. in press-a). In the same study, only iv atropine sulfate produced a significant impairment in escape latency. Atropine sulfate (50 mg/kg, ip) impaired spatial discrimination accuracy (but not escape latency), in rats who previously had achieved asymptotic performance under drug-free conditions (Hagan et al. 1986). Hagan et al. (1986) concluded that there were quantitative differences in the effects of cholinergic blockade when administered prior to training and when administered to well-trained rats; the latter were less sensitive.

In light of the previous research, there appears to be considerable variability on the effects of cholinergic blockade on the retention of a well-learned spatial task. The present study was undertaken to determine the effects of different levels of cholinergic blockade, with a broad dose range of atropine sulfate, on the retention of an overtrained spatial task in the Morris water maze.

MATERIALS AND METHODS

Subjects. Twelve experimentally naive adult male Charles River CD strain rats, with a mean age of 140 days (300-500g) at the time of testing served as subjects. All rats were housed individually in hanging wire mesh cages with ad-lib access to food and water. Behavioral testing was conducted between 0900 and 1500 hours.

Apparatus. The rats were trained and tested in a Morris water maze (Morris 1981). The water maze consisted of a circular black fiberglass pool measuring 134 cm in diameter X 50 cm in height and filled to a depth of 30 cm with water (28° C). The water was rendered opaque with blue food coloring. A circular stainless steel escape platform, 10 cm in diameter at the top and base, was painted black. The escape platform was 1 cm below the surface of the water and always positioned in the center of the southeast quadrant of the pool. Two start positions were located on the perimeter of the pool: one in the north, the other in the west, at approximately a 45° angle equidistant from the escape platform. The maze was illuminated by overhead lights and the testing room contained numerous extramaze cues such as a laboratory table, sink and chair.

Spatial Learning Procedure. Prior to the first week of training the animals were handled each day for approximately three minutes. One day before training each animal was placed in the pool with no escape platform and allowed to swim for 90 s. The animals were then returned to their home cages. On training days animals were trained ten trials per day for six days. The start position (north vs west) was randomized for each animal, across trials, but the submerged escape platform was always fixed in the

center of the southeast quadrant. A trial started when the rat was immersed in water and held with his head facing the wall of the pool at one of the two starting locations. Each animal was allowed 120 s to escape onto the platform. If the animal failed to escape within this time it was guided to the platform. Whether or not the animal had escaped or been guided to the platform, it remained there for 15 s before being removed and placed in the home cage for a 10 min inter-trial interval. Escape latency was recorded for each trial. All rats were trained to asymptotic performance prior to the administration of atropine sulfate.

Atropine Administration and Spatial Retention Procedure. On treatment days the animals received ip injections of 5, 25, 50, 75 and 100 mg/kg of atropine sulfate or an equivalent volume of saline as a control. The atropine sulfate (Sigma Chemical Co., St. Louis, MO) was dissolved in 0.2 ml of sterile saline. Each animal was injected and spatial retention assessed over six separate test days. Two control days, during which each animal received five undrugged trials in the water maze, were inserted between treatment days. The treatment order was counterbalanced according to a Latin-square design. Every animal received every treatment once and each animal received only one treatment per test day. Thirty minutes prior to testing, each animal was injected and returned to their home cage to await testing. Ip injections were made into the peritoneum lateral to the midline in the center of the abdomen. A 50 mg/kg, ip dose of atropine sulfate was selected since it has been shown to alter forebrain acetylcholine release (Dudar et al. 1979), forebrain electroencephalographic activity (Vanderwolf 1975), motor behavior (Schallert et al. 1980) and produce virtually complete occupation of muscarinic binding sites in the rat brain (Yamamura et al. 1974). A dose of 100 mg/kg, ip, which represents twice the dose-effect

established for 50 mg/kg, ip, was used as the upper limit of the dose range. A dose of 5 mg/kg, ip is inadequate to produce these central cholinergic changes and was therefore used as the lower dose.

Spatial retention was assessed by measuring escape latency, heading error, swim speed, swim distance and swim path. The animals' swims were videotaped with a Sony videorecorder placed above the center of the maze. A videotape of each swim was played to trace swimming paths onto a paper map. Swimming paths for each rat were also recorded on a map of the maze by an experimenter seated by the pool's edge. Maps traced from the videotape were placed on a translucent digitizing tablet, 44 x 44cm (Altek Corp. Model No. R-22; Silver Springs, MD) and a cursor with a magnetic search coil was used to trace movement and position. The movement and position of the animal was digitized by an AC 40 DKF controller (Alteck Corp.; Silver Springs, MD). Heading error was calculated by modifying the procedure described by Whishaw (1985). An 18-cm-wide path from the start point to the center of the platform was designated an error-free alley. If the animal swam outside the alley over the initial 12 cm of the swim it received a maximum of one error. A swim path measure was devised to assess the pattern of movement to reach the platform. Animals which swam a linear or curvilinear path to the platform were scored as correct. If the animal reversed itself, while swimming to the platform, by making one or more 360° circles and thereby looping to the platform it received a maximum of one error on that trial.

RESULTS

Spatial Training

Repeated measures analysis of variance was performed on escape latencies over trials during the training phase of the study. Throughout training, (i.e., days 1-6), all animals rapidly learned to swim to the hidden escape platform. Over 60 trials the mean escape latency declined from 90 to 4 seconds. There was a significant effect of training trials on escape latency, F (59,649) = 10.31, $p < .001$. All animals learned to swim a straight (linear) path to the escape platform.

Spatial Retention After Atropine Sulfate Administration

The analysis of spatial performance after treatment with atropine sulfate was performed using a repeated measures analysis of variance. The single factor in the analysis was drug dose (6 levels: 5, 25, 50, 75 and 100 mg/kg, ip atropine sulfate and the equivalent volume of saline).

The analysis of variance revealed a significant drug dose effect on escape latency, F (5,55) = 2.62, $p < .05$. Post hoc Newman-Keuls ($p < .05$) comparisions of drug dose means revealed a significant difference in escape latency only between the 100 mg/kg atropine sulfate dose and the saline control. The analysis of heading errors showed no significant drug dose effect. There was a significant drug dose effect on swim distance, F (5,55) = 2.49, $p < .05$. Newman-Keuls analysis showed the mean swim distance for the 50, 75 and 100 mg/kg atropine sulfate doses to be significantly greater than the saline control. Escape latencies and swim distances for each drug dose are shown in Figure 1. Latency and distance are similiar but not identical measures of spatial performance.

The analysis of swim speed (cm/sec) showed a statistically significant drug dose effect, F (5,55) = 3.53, $p < .01$. Newman-Keuls follow-up analyses showed that the 75 and 100 mg/kg atropine sulfate treated animals swam significantly slower than the saline treated animals. The results of the swim speed measure are shown in Figure 2. The analysis of variance also revealed a significant drug dose effect on swim path, F (5,55) = 5.79, $p < .001$. Newman-Keuls analysis showed that the atropine sulfate treated animals (5, 25, 50, 75 and 100 mg/kg dose levels) reached the platform by swimming toward its position but frequently looping 360° at least once until the platform was reached. The looping strategy was usually within the designated alley leading directly to the platform. The saline treated animals never looped and swam a straight (linear) path to the platform. Figure 2 shows the number of animals swimming looping patterns to locate the platform for each dose level.

Figure 3 shows the swim patterns of one animal treated with each dose of atropine sulfate and the saline control. When treated with the various doses of atropine sulfate, the rat swam initially toward the platform but frequently stopped short and looped 360° then continued on a similiar heading until the platform was reached. There was no significant difference between clockwise and counter-clockwise generated loops among the atropine treated rats exhibiting this behavior.

DISCUSSION

This study shows that atropine sulfate impairs overtrained spatial performance in a dose-dependent fashion. Our data support previous findings (Hagen et al. 1986; Rauch et al. in press-a; Rauch et al. in press-b) showing that cholinergic blockade with atropine sulfate disrupts spatial performance when administered prior to retention testing.

Atropine sulfate also slowed the performance of rats in a dose-dependent manner. Our results are similiar to the effect of scopolamine on spatial performance in rats (Eckerman et al. 1980; Okaichi and Jarrard 1982) and to the effect of atropine sulfate on spatial performance in mice (Levy et al. 1983). Although in the present study a minimal effective dose of 100 mg/kg, ip of atropine sulfate was required to significantly impair escape latency (when compared to the saline treatment), the overall pattern of results suggests that escape latencies increased in a dose-dependent fashion. Moreover, swim speed (cm/sec) also slowed in a dose-dependent fashion; with a minimal effective dose of 75 mg/kg, ip necessary to significantly differ from the saline treatment. Levy et al. (1983) concluded that a large component of the rate-slowing effect of atropine sulfate found in their study might have been due to peripheral effects which are not centrally mediated; the slowing effect was significantly increased by atropine methylnitrate as well as atropine sulfate. However, this is contrary to the findings of previous studies reporting that cholinergic antagonists impair the performance of trained animals in spatial tasks by a central mechanism (Buresova and Bures 1982; Eckerman et al. 1980; Hagan et al 1986).

In the present study atropine sulfate did not significantly increase heading errors; atropine treated rats always swam directly toward the escape

platform over the first 12 cm of their swim path. However, after the initial 12 cm, their swim path toward the platform would consist of numerous 360° loops until the platform was reached. O'Keefe and Nadel (1978) have suggested that rats use three strategies for spatial navigation. First, a place or spatial-mapping strategy is used when the relational properties of distal cues are used to locate a hidden platform. Second, a cue strategy is used when navigation to the hidden platform is guided by approaching a dominant cue. Lastly, a praxis strategy is used when navigation to the hidden platform is based on a sequence of movements, such as turn right and then turn left. Rats may use all three strategies to solve a spatial problem (Whishaw and Mittleman 1986).

Rats normally develop a map of the pool based on distal 'extramaze' cues and they use a spatial-mapping strategy to direct some portion of their swims (Morris et al. 1982; Schenk and Morris 1985; Whishaw and Tomie 1987; Sutherland et al. 1983). However, will the same mapping information acquired in the normal ('undrugged') training condition be retrieved to solve a spatial problem after cholinergic blockade? In the present study, the processing or recall of distal extramaze cues may have been impaired by the atropine sulfate. In fact, atropinized rats have difficulty processing the relational properties of distal cues (Sutherland et al. 1982; Whishaw and Tomie 1987) and reducing the number of available distal cues impairs acquisition of accurate place navigation (Sutherland and Dyck 1984). In our study, even the lowest dose of atropine sulfate (05 mg/kg, ip) produced a looping strategy to the platform. Since spatial strategies acquired in a normal condition are used in the drugged condition (Whishaw and Tomie 1987) there may be an incongruence between the relational properties of distal cues being acquired and processed under cholinergic blockade and the map of distal cues constructed during acquisition. Hence, the atropinized rats

appear to recall the general position of the platform but have to explore or 'loop' to determine its precise location.

The impairment in spatial processing shown by the atropine treated animals may also be due to a direct effect of atropine on the visual system. In a human study Haegerstrom-Portnoy et al. (1987) reported a long lasting, dose-related increase in pupillary diameter and decrease in accommodative amplitude with accompanying loss of near visual acuity (at a distance of 40 cm) following administration of atropine sulfate (2 and 4 mg/70kg^{-1} body weight, im). Moreover, in another human study this difficulty in near vision was dose dependent: 39 percent of subjects cited difficulty after 2 mg, 40 percent after 3 mg and 100 percent after 4 or 5 mg (Headley 1982). Levy et al. (1983) reported large mydriatic effects in mice over 6 hours following injection of doses above 1 mg/kg of atropine sulfate. However, atropine effects on both accuracy and run time, in the radial arm maze, disappear within 3 hr post-injection. They concluded that the perception of distal cues is probably not affected by mydriasis (Levy et al. 1983).

In summary, the retention of an overtrained spatial task assessed by traditional measures of spatial navigation, escape latency, heading error, swim distance and swim speed show some impairment with cholinergic blockade. A relatively low dose of atropine sulfate (5 mg/kg, ip) significantly disrupts the normal strategy used to locate a previously acquired spatial response. As a result, atropinized animals frequently adopted a looping strategy to find the platform. We suggest that cholinergic blockade may significantly disrupt the processing of the relational properties of distal visual cues which rats use in place navigation.

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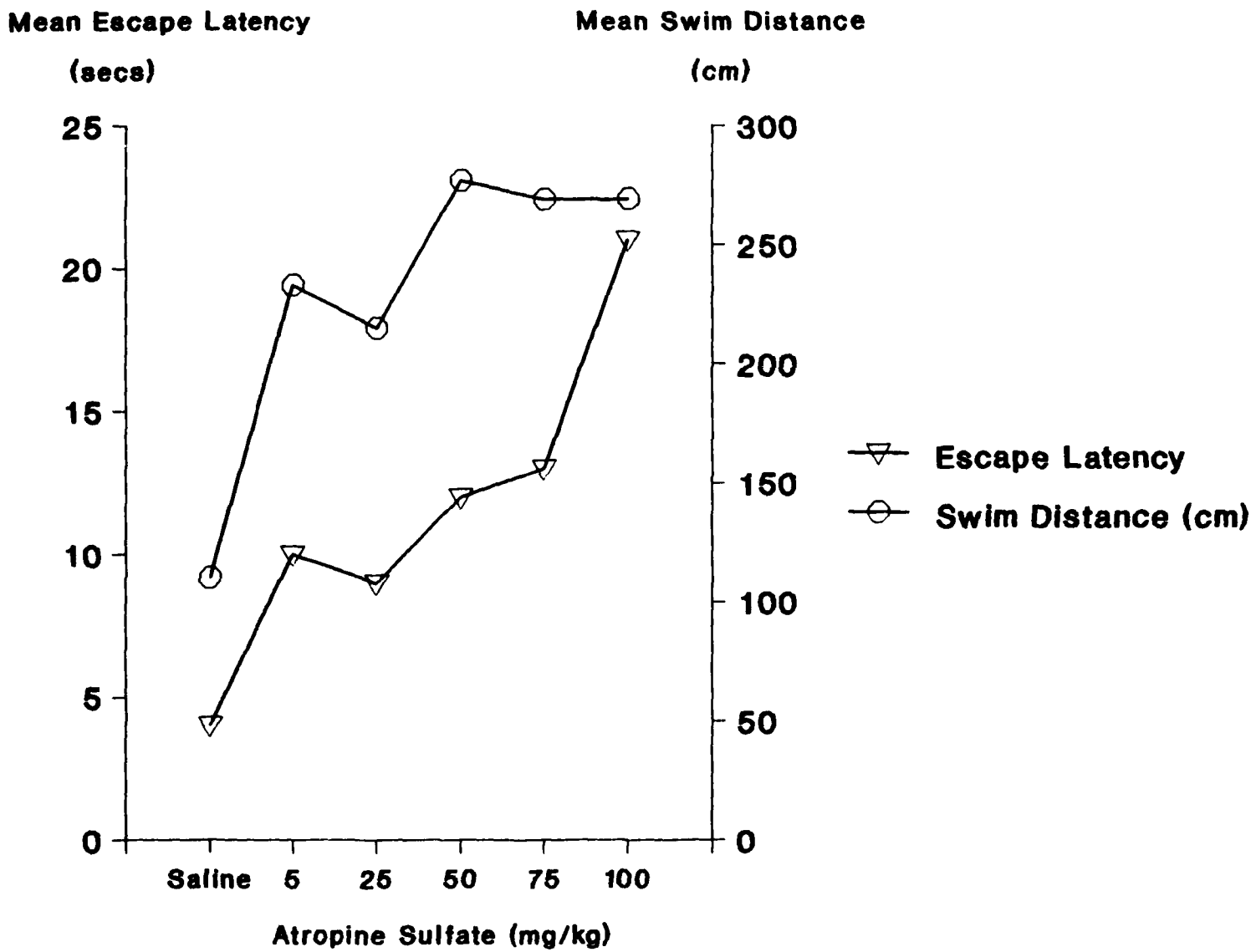
Fig. 1. Mean escape latencies and swim distances as a function of the dose of atropine sulfate.

Fig. 2. Mean swim speed (cm/sec) and the number of animals swimming looping paths to locate the escape platform as a function of the dose of atropine sulfate.

Fig. 3. Swim paths of one rat treated with each dose of atropine sulfate and the saline control. Atropine sulfate did not significantly effect heading error. However, atropinized rats frequently employed a looping strategy to locate the platform.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Mean Swim Distance
(cm)
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15
10
5
0
300
250
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50
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5
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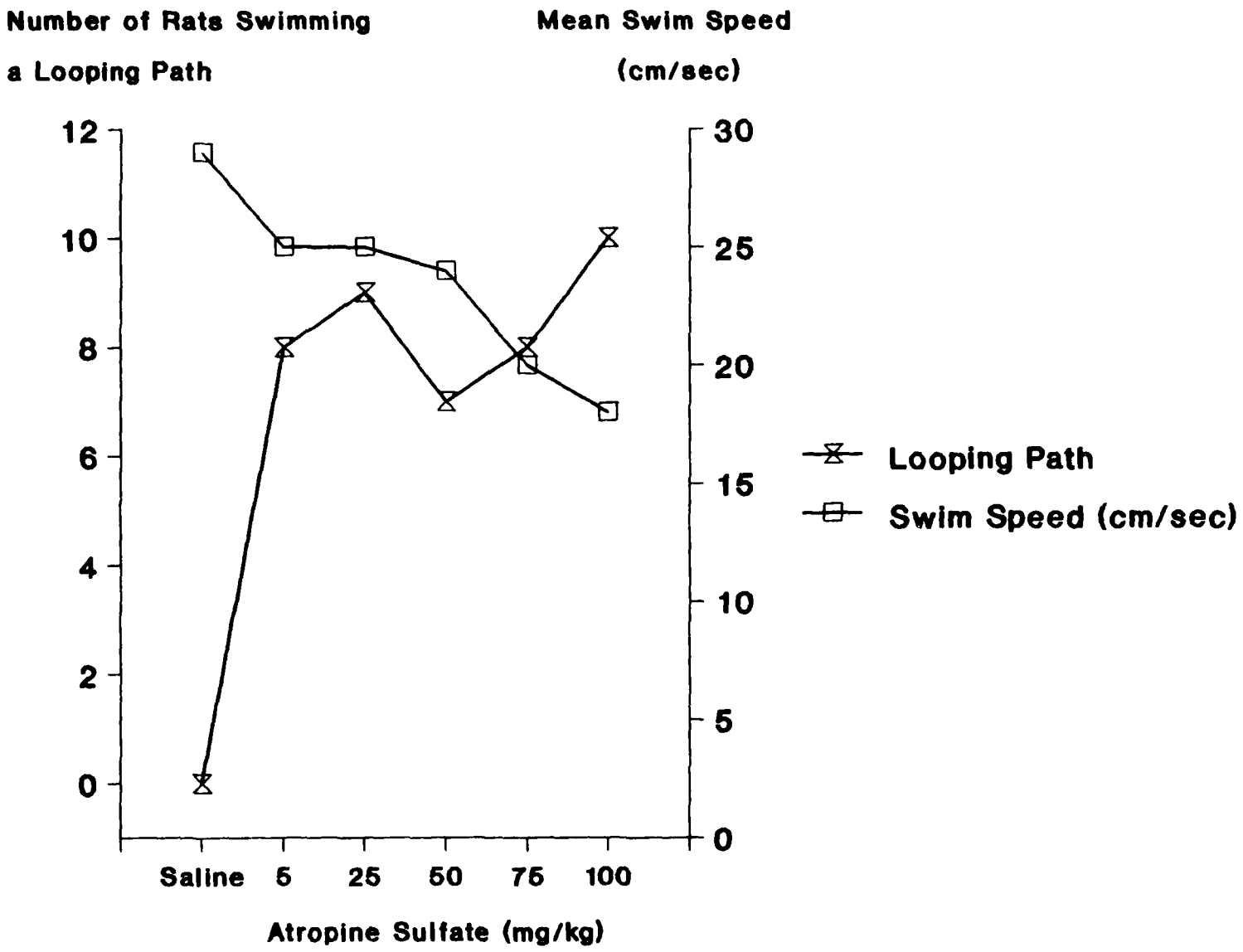
Atropine Sulfate (mg/kg)
Escape Latency
Swim Distance (cm)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(cm/sec)
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10
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6
4
2
0
30
25
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Saline
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Atropine Sulfate (mg/kg)
Looping Path
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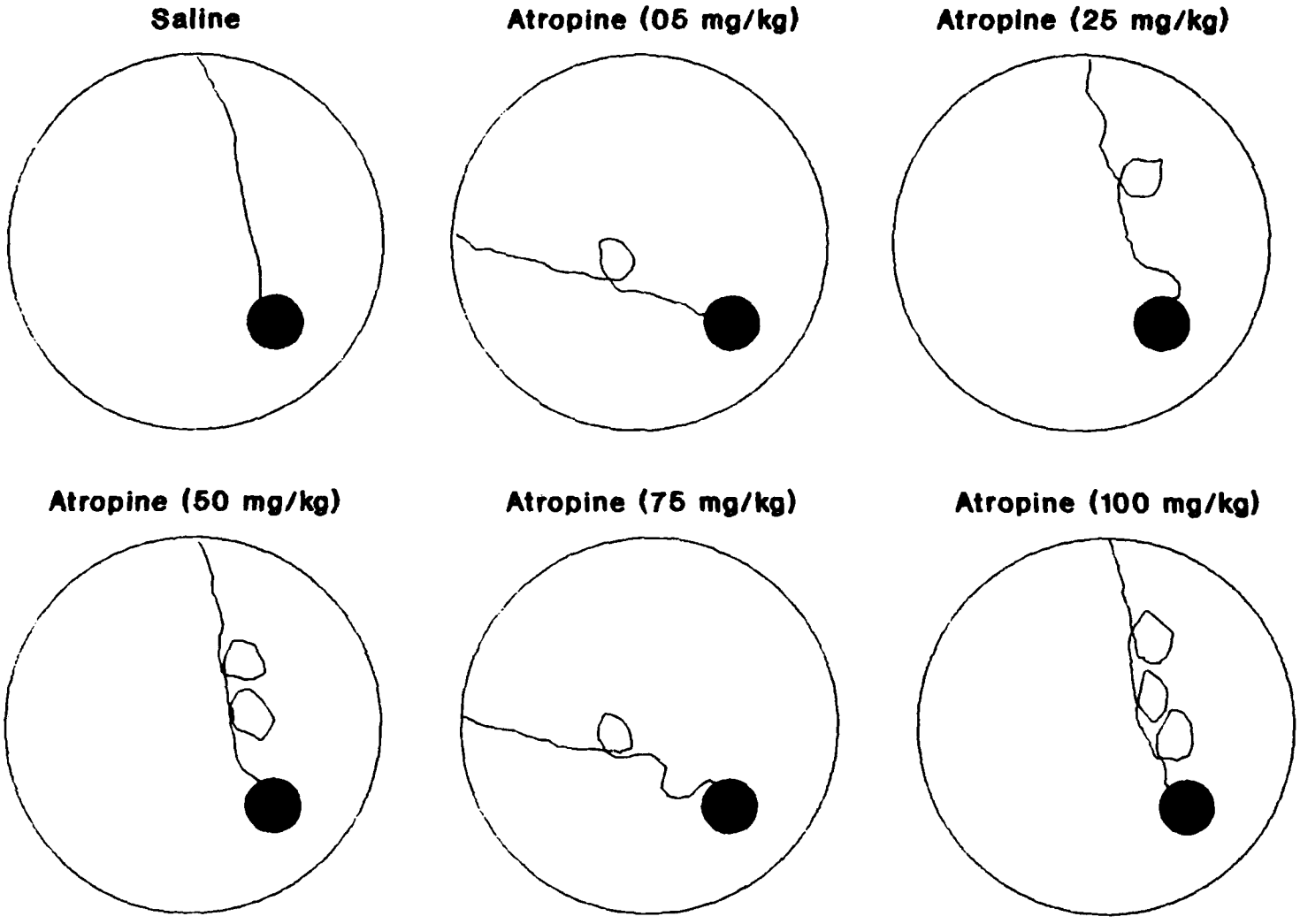
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